IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Atty. Docket No. 06-796)

In the Application of:	)	
	)	
Fanara et al.	)	
	)	Examiner: Timothy P.
Thomas		
Serial No. 10/599,451	)	
	)	Art Unit: 1614
Filing Date: September 28, 2006	)	
	)	Confirmation No.: 9142
For: Pharmaceutical Composition of Piperazine Derivatives	)	

DECLARATION OF DOMENICO FANARA UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Domenico Fanara, in support of the above-identified patent application, do aver and state as follows:

1. I am the first named inventor of this application.
2. I received a Pharmacy degree from University of Liège Belgium in 1986
3. I have been employed by UCB Pharma SA since 1993 after having spent 6 years in another pharmaceutical company Galephar S.A as head of formulation development.
4. A copy of my CV is attached hereto as Exhibit A that include list of publications
5. Levocetirizine and particularly its dihydrochloride salt are known to be useful as antihistamines. Levocetirizine dihydrochloride is available in solid dosage form. The present invention is directed to a formulation that allows for the availability of levocetirizine and its salts in liquid dosage form.

6. One common problem with liquid pharmaceutical formulations in general is that the presence of water can allow for the growth of microorganisms, particularly after the seal on the product packaging has been broken, and when the contents of the packaging are exposed to dosing implements. Thus, it has become common practice to include preservatives in such formulations to prevent the growth of such microorganisms. Methyl parahydroxybenzoate and propyl parahydroxybenzoate, commonly known as methyl paraben and propyl paraben, respectively (hereinafter "MP" and "PP," together "parabens"), are frequently used for this purpose.

7. The combined parabens in typical pharmaceutical preparations is at least about 2 mg/ml, as shown by an accepted pharmaceutical treatise (see, Remington, The Science and Practice of Pharmacy, 21st ed., 2005, pp. 748-749, Ex. B, hereinafter "the Remington treatise").

8. In the course of developing liquid pharmaceutical formulations of levocetirizine and its salts, we were surprised to discover that levocetirizine itself can act as an anti-microbial. This is shown in Tables 5 and 6 of the present application, in which samples of an oral solution and oral drops containing 0.5 and 5.0 mg/ml of levocetirizine hydrochloride, respectively, and which were inoculated with various microbes, were essentially free of bacteria 14, 21, and 28 days after inoculation. The oral drop formulation that contained the higher concentration of the drug also was substantially free of fungal infection 21 and 28 days after inoculation.

9. This result was totally unexpected. Even though levocetirizine and its salts were well characterized, to our knowledge it had not been recognized prior to our invention that levocetirizine has antimicrobial properties. This led to our discovery that liquid pharmaceutical compositions of levocetirizine could be formulated with lower paraben concentrations than previously thought necessary and without additional preservatives.

10. Submitted herewith as Exhibit C are the results of testing of antimicrobial efficacy on several batches of oral drop solution having 5 mg/ml of levocetirizine, 0.3375 mg/ml MP and 0.0375 mg/ml of PP, for an MP/PP ratio

of 9 and a total parabens content of 0.375 mg/ml. The compositions contained no other preservative. The batch sizes varied from 100 L to 1000 L. The testing results confirmed that inoculated test samples of all of the batches were essentially free of both bacteria and fungus 14 and 28 days after inoculation. This result is surprising because the amount of parabens used was less than one fifth of the minimum recommended by the Remington treatise.

11. Submitted herewith as Exhibit D are the results of testing of antimicrobial efficacy on two batches of oral solution containing 0.5 mg/ml of levocetirizine, 0.675 mg/ml MP and 0.075 mg/ml of PP, for an MP/PP ratio of 9 and a total parabens content of 0.750 mg/ml. The compositions contained no other preservative. The batch sizes were each 1000 L. The testing results confirmed that inoculated test samples of both of the batches were essentially free of bacteria and two of three species of fungus 14 and 28 days after inoculation. This result is surprising because the amount of parabens used was less than one half of the minimum recommended by the Remington treatise.

12. I have reviewed the references cited by the U.S. Patent and Trademark Office against this application.

13. WO 02/47680 of DeLongueville et al. relates to earlier work on cetirizine and its optically active isomers, performed by the present assignee. The only mention of any specific preservative is at page 6, lines18-22, which states, "As an example of a composition according to the present invention, the following formulation of a syrup (oral drops) is preferred: cetirizine dihydrochloride, methyl- and propyparaben, saccharinum, and purified water." There is no teaching or suggestion as to the relative amounts of any of these components of the composition. As one skilled in the art, upon reading this disclosure I would understand that the amount of total parabens intended was at least the minimum of 2 mg/ml as set forth in the Remington treatise and as generally understood at that time as being a typical concentration of preservative for a liquid pharmaceutical product.

14. Gilliland et al., *J. Applied. Bacteriology*, 1992, 72, 252-257 ("Gilliland 1"), reports a study on the effect of temperature on the kill rate of *E. coli* by methyl and propyl parabens. Solutions containing 0.12% MP (1.2 mg/ml) and 0.012% PP (.12 mg/ml) were evaluated at temperatures of 34, 37, 40, and 42°C, which are well beyond the temperatures at which most pharmaceutical compositions are stored. The combined parabens in the tested solutions was 1.32 mg/ml, more than 10% higher than the 1.125 mg/ml maximum parabens concentration of our invention. The longest time period over which measurements were made was 28 hours (Fig. 5) so that the results cannot be properly extrapolated to pharmaceutical compositions which require long-term storage. No pharmaceutical component of any type was included in the formulations evaluated. In a test run in which the temperature of the sample was constantly altered rather than being held at a steady state, the authors found that the viable count of *E. coli* showed variability that was too high to enable adequately precise rate constants to be calculated, such that the method was of little value in that experiment (p. 257). The amount of parabens used in Gilliland 1 is outside the claims of our invention; the experiments of Gilliland were conducted at different temperatures, and for much shorter times than the experiments of our application. For at least these reasons, as one skilled in the art, it is my opinion that Gilliland I would be afforded little weight by those of ordinary skill in the art with respect to its relevance to the present invention and does not teach or suggest a pharmaceutical solution of levocetirizine or one of its salts, and with a combined parabens of no more than 1.125 mg/ml.

15. Gilliland et al., *J. Applied. Bacteriology*, 1992, 72, 258-261 ("Gilliland 2"), reports a study on whether methyl and propyl paraben act synergistically. Various solutions were prepared with MP at either 0.12% or 0.14%, and with PP at 0.012% and 0.014%. These concentration levels were selected because at these levels the kill rate was slow enough that the rate constants could be calculated; higher concentrations killed bacteria too quickly for the required sampling to be carried out satisfactorily. (p. 259) To me, as one skilled in the

art, this suggests that the concentrations selected for study were not necessarily optimal for use in a pharmaceutical composition that have to be essentially free of such bacteria. I also note that the time period over which testing was done was about six hours, so that the results cannot be properly extrapolated to pharmaceutical compositions which require long-term storage.

16. Doron discloses compositions that significantly reduce E.coli, but at paraben concentration that are 37% and 248% greater than the concentrations used in our invention. As one skilled in the art, this reference suggests to me that at the MP/PP ratios of Doron, a much greater total concentration of parabens is necessary to achieve a composition that remains substantially free of bacteria than was achieved with our invention.

17. As one skilled in the art, the combination of Doron, DeLongueville, Gilliland I and Gilliland II does not teach or suggest that a pharmaceutical formulation could be prepared that is maintained substantially free of bacteria and having the a total of MP and PP of no greater than 1.125 mg/ml, and no other preservative. Gilliland I and II were thermal and kinetic studies of parabens. The authors indicate that the concentrations chosen were those that facilitated their measurements; there is no suggestion that the concentrations chosen for evaluation in these studies would be suitable for use in actual pharmaceutical compositions.

I hereby state that I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001), and that such willful false statements may jeopardize the validity of the application or document or any registration resulting therefrom, and I declare that all statements made of my own knowledge are true; and all statements made on information and belief are believed to be true.

Domenico Fanara

Date: 23/11/2010

EXHIBIT A

Domenico Fanara, Ind. Pharm.

Inte

Home Address: Rue Pont de Soleil, 2A,
B-4520 Wanze

Telephone (wk): +32.2.386.20.04
Telephone (hm): +32.85.23.57.69
Mobile : +32.494.578.142
E-mail: domenico.fanara@ucb.com

Current Position: Senior Director
Innovation & Technology Development
UCB Pharma S.A.
B-1420 Braine-l'Alleud.

Date of birth: October 11th, 1963

Expertise: Specific Skills

- Fully familiar with pharmaceutical sciences and drug development.
- Extensive experience in the development of novel technologies for compounds with poor solubility
- Extensive experience in the development of slow release formulations
- Evaluation of external technologies to support own projects
- Program and project management skills including goal setting, planning, budget forecasting and tracking and progress reporting
- Experience in management of development staffs with global footprint.
- Management of budget (OPEX,External,Investment)

Strengths:

- Creativity, focus, and result oriented

General skills:

- Trilingual English, French (mother tongue) Italian
- Fully familiar with the main computer softwares (Word, Excel, PowerPoint, Access, Outlook ...)

Domenico Fanara, Ind. Pharm.

Employment:

April 2010	Senior Director Head of Innovation and Technology Development
2009	Delivery Route R&D Senior Director and Deputy of the head of pharmaceutical Sciences UCB Pharma S.A. (85 FTE's)
2006 -2009	Drug Product R&D Senior Director, UCB Pharma S.A. (135 FTE's)
1995	Manager of Pharmaceutical Development, UCB Pharma
1993	Galenic Development, UCB Pharma
1988	Head of Pharmaceutical Development, SMB – Galephar
1986	Pharmaceutical Development, SMB – Galephar

Current key and past accountabilities:

To support a harmonized consistent approach to new technologies development
To support the development of new tools, new technologies to optimize processes .
To participate in the integration of innovation in the design of the future manufacturing processes (Chemical DS, Chemical DP, Biological DS, Biological DP, analytical Tools).
To develop internal expertise and competences at UCB for these novel technologies

The key requirement of my function is the management of all activities of the Drug Product and Delivery Route Research & Development department in accordance with the Pharmaceutical Sciences mission statements.

The fulfilment of this role will therefore require the active provision of strategic technical guidance for the initiation and management of development projects and for the supply of Drud Product (DP) for early clinical trials. In connection with this, I ensure the management of the department via the effective management of resources (specifically staff, facilities and the relevant budgets).

- To lead pharmaceutical development globally encompassing all projects from the Research to Development transition point through proof of concept transition into DP D&I Department. The DP R&D Department will also be responsible for transferring processes, technology, data and preparing regulatory submissions with its business partner DP DI (Global Technical Operations). (The role has a global remit and must ensure the optimal use of resources across UCB for all projects. This is a line function and I'm a member of the Pharmaceutical Sciences and NonClinical Management Team).

Domenico Fanara, Ind. Pharm.

As deputy of the head of Pharmaceutical Sciences :

- To coordinate Development's activities related to Pre-formulation ,Formulation & Drug Delivery Developments for NBE's and NCE's
- To manage the availability of DP for Clinical trials.
- To obtain and to ensure the coherence between all different Projects, in order to prioritize responsibilities and tasks in the department.
- To ensure full compliance with QA, cGMP or related requirements.
- To strengthen the UCB IP position through innovation.
- I oversee and advice for the development of pre-clinical and clinical formulations and characterization of materials as well as development of manufacturing processes for all products in the portfolio.

I am also responsible for managing the:

- Development of intellectual property fillings with for freedom to operate and potential exclusions.
- Development of extensions for current UCB proprietary drug delivery technologies.

Education:

1989 Industrial Pharmacist
1986 Pharmacist, University of Liège, Belgium
1981 Humanities (applied sciences section), Provincial Institute of secondary Education, Seraing, Belgium.

Domenico Fanara, Ind. Pharm.

Other Relevant courses and workshops attended:

2008 Global Leadership program

2008 Leadership and innovation

2007 Internal training on NBE's

2004 – 2005 Leadership and Management – Internal Training

2001 Change management – Internal Training

2000 Management by objectives – Internal Training

1999 UCB Global leadership program – Internal Training

1998 Experimental planification – Internal Training

1998 Goal directed project management – Internal Training

1998 Compression: simple and double layer tablets (Courtoy)

1997 New drug delivery systems (P. Couvreur)

1996 Symposium drug delivery

1995 Pharmaceutical technology: lipidic vehicles (Gattefosse)

1995 Pharmaceutical technology conference (Amsterdam)

1995 First european intensive course on new forms a,nd new routes of administrations or drugs (Coimbra)

1994 GTRV (Paris)

1994 Pharmaceutical technology conference (Barcelona)

1993 Statistic course (ULB)

1993 European congress of biopharmaceutics and pharmacokinetics

1993 – 1995 Experimental work of a PHD Thesis – "Oral drug delivery of peptides" (ULB)

1992 Peptide and protein drug delivery (V. Lee)

1986 Work experience in the pharmaceutical chemistry laboratory of the University of Liège (Prof. Delarge)

1985 Work experience in the clinical biology laboratory of the University of Liège Prof. Heusghem)

Domenico Fanara, Ind. Pharm.

Bibliography (literature & patents)

Literature

Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine.
Source
International Journal of Pharmaceutics. 299(1-2):167-77, 2005 Aug 11.

Correlation of extrusion forces, raw materials and sphere characteristics.
Source
Journal of Pharmacy & Pharmacology. 44(8):676-8, 1992 Aug.

Instrumentation of a gravity feed extruder and the influence of the composition of binary and ternary mixtures on the extrusion forces.
Source
Journal of Pharmacy & Pharmacology. 43(11):745-9, 1991 Nov.

Preparation and in vitro/in vivo evaluation of nano-sized crystals for dissolution rate enhancement of UCB-35440-3, a highly-dosed poorly water soluble weak base.
Eur. J. Pharm. & Biopharm, 64, 360-368 (2006)

In vitro transport studies of nifedipine nanoparticules across Caco-2/HT29-5M21 cultures & co-cultures
Eur. J. Pharm. & Biopharm, submitted, (2007)

Patents

Tablet comprising cetirizine and pseudoephedrine
International patent application WO 03/002098 and US Patent 7,014,867

Pharmaceutical compositions for controlled release of active substances
International patent application WO 98/41194 and US Patent 6,699,502

Pseudopolymorphic forms of 2-[2-[4-[Bis (4-fluorophenyl) methyl]-1-piperazinyl]ethoxy]acetic acid dihydrochloride
International patent application WO 99/28310 and US Patent 6,335,331

Tablet comprising efletirizine and pseudoephedrine.
International patent application: WO 2003/059328

Tablet comprising efletirizine
International patent application: WO 2003/057198

Oral formulations for cetirizine and related compounds.
International patent Application: WO 99/01133 and US patent US 6,455,533

Domenico Fanara, Ind. Pharm.

Pharmaceutical compositions for oral administration comprising substituted benzhydrylpiperazines and a cyclodextrin.
US Patent US 6,455,533 - European Patent EP 0 994 710.

Use of pharmaceutical compositions capable of being gelled in periodontology
International patent application WO 56726 and US Patent US 6,818,224

Pharmaceutical compositions capable of being gelled
International patent application WO 99/56725 and US Patent US 6,464,987

Pharmaceutical composition of piperazine derivatives.
International patent application WO 2006/005507

Pharmaceutical compositions comprising Levetiracetam
International patent application WO 2010/006929

Liquid composition of Brivaracetam
International patent application WO 2009/109547

Pharmaceutical compositions comprising 2-oxo-1-pyrrolidine derivatives
International patent application WO 2010/086315

Pharmaceutical compositions comprising Brivaracetam
International patent application WO 2010/089372

Pharmaceutical oral compositions
International patent application WO 2010/057869

Pharmaceutical oral compositions
International patent application WO 2010/057870

Other interests:

Reading, cycling, swimming.

EXHIBIT B

21ST EDITION

Remington

The Science and Practice of Pharmacy

LIPPINCOTT WILLIAMS & WILKINS
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AUTHORS

The 133 chapters of this edition of *Remington* were written by the editors, by members of the Editorial Board, and by the authors listed on pages xi to xv.

Director

Philip P Gerbino 1995-2005

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1 2 3 4 5 6 7 8 9 10

When a preservative is required, its selection is based upon several considerations, in particular the site of use whether internal, external, or ophthalmic.[13] Several researchers have described various interactions that must be considered when preservatives are selected.[14,15] The major criteria that should be considered in selecting a preservative are as follows: It should be effective against a wide spectrum of microorganisms, stable for its shelf life, nontoxic, nonsensitizing, compatible with the ingredients in the dosage form, inexpensive, and relatively free of taste and odor.

The chosen preservative should be sufficiently stable and soluble to achieve adequate concentration to provide protection. This choice is more critical in two and three phase emulsion systems in which the preservative may be more soluble in the oil phase than in the aqueous phase.[12,16] The pH of the preparation must be considered to ensure that the preservative does not dissociate rendering it ineffective or degrade by acid or base catalyzed hydrolysis. The undissociated moiety or molecular form of a preservative possesses preservative capacity because the ionized form is unable to penetrate microorganisms. The preservative must be compatible with the formulation ingredients and the product container or closure. Finally, the preservative must not impact the safety or comfort of the patient when administered. For instance, preservatives used in ophthalmic preparations must be non-irritating. Chlorobutanol, benzalkonium chloride, and phenylmercuric nitrate are commonly used in these applications.

Although few microorganisms are viable below a pH of 3 or above pH 9, most aqueous pharmaceutical preparations are manufactured within the favorable pH range. Acidic preservatives such as benzoic acid, boric acid, and sorbic acid are less dissociated and more effective in acidic formulations. Similarly, alkaline preservatives are less effective in acidic or neutral conditions and more effective in alkaline formulations. The scientific literature is rife with examples of incompatibilities between preservatives and other pharmaceutical adjuncts.[17–19] Commonly used macromolecules including cellulose derivatives, polyethylene glycol and tragacanth gum have been reported to cause preservative failure due to binding and adsorption.[20,21]

The mode of action by which preservatives interfere with microbial growth, multiplication, and metabolism occurs through one of several mechanisms. Preservatives often alter cell membrane permeability causing leakage of cell constituents (partial lysis), complete lysis, and cytoplasmic leakage and / or coagulation of cytoplasmic constituents (protein precipitation). Other preservatives inhibit cellular metabolism by interference with enzyme systems or cell wall synthesis, oxidation of cellular constituents, or hydrolysis.

Preservatives commonly used in pharmaceutical products are listed in Table 39-2 with typical concentration levels. Preservatives may be grouped into a number of classes depending upon their molecular structure. These basic groups are discussed below.

Alcohols

Ethanol is useful as a preservative when it is used as a solvent; however, it does need a relatively high concentration, somewhat greater than 15%, to be effective. Too high a concentration may result in incompatibilities in suspension and emulsion systems. Propylene glycol also is used as a solvent in oral solutions and topical preparations, and it can function as a preservative in the range of 15% to 30%. It is not volatile like ethanol and is used frequently not only in solutions but also in suspensions and emulsions. Chlorobutanol and phenylethyl alcohol are other alcohols used in lower concentrations (about 1%) as preservatives.

Acids

Benzoic acid has a low solubility in water, about 0.34% at 25°C, but the apparent aqueous solubility of benzoic acid may be enhanced by the addition of citric acid or sodium acetate to the solution. The concentration range used for inhibitory action varies from 0.1% to 0.5%. Activity depends on the pH of the medium because only the undissociated acid has antimicrobial properties. Optimum activity occurs at pH values below 4.5; at values above pH 5, benzoic acid is almost inactive.[22] It has been reported that antimicrobial activity of benzoic acid is enhanced by the addition of the basic protein protamine.[23] Sorbic acid also has a low solubility in water, 0.3% at 30°C. Suitable concentrations for preservative action are in the range of 0.05% to 2%. Its preservative action is due to the nonionized form; consequently, it is only effective in acid media. The optimum antibacterial activity is obtained at pH 4.5, and practically no activity is observed above pH 6. Sorbic acid is subject to oxidation, particularly in the presence of light and in aque-

Table 39-2. Common Preservatives Used in Liquid Pharmaceutical Dosage Forms and Their Typical Concentration Levels

ANTIMICROBIAL PRESERVATIVES	TYPICAL USAGE LEVEL (% W/W)	ANTIFUNGAL PRESERVATIVES	TYPICAL USAGE LEVEL (% W/W)
Benzalkonium Chloride	0.002–0.02%	Butyl Paraben	0.1–0.4%
Benzethonium Chloride	0.01–0.02%	Methyl Paraben	0.1–0.25%
Benzyl Alcohol	3.0%	Ethyl Paraben	0.1–0.25%
Bronopol	0.01–0.1%	Propyl Paraben	0.1–0.25%
Cetrimide	0.005%	Benzoic Acid	0.1–0.5%
Cetylpyridinium chloride	0.0005–0.0007%	Potassium sorbate	0.1–0.2%
Chlorhexidine	0.002–0.5%	Sodium Benzoate	0.1–0.2%
Chlorobutanol	0.5%	Sodium Propionate	5–10%
Chlorocresol	0.2%	Sorbic Acid	0.05–0.2%
Chloroxylenol	0.1–0.8%		
Cresol	0.15–0.3%		
Ethyl Alcohol	15–20%		
Glycerin	20–30%		
Hexetidine	0.1%		
Imidurea	0.03–0.5%		
Phenol	0.1–0.5%		
Phenoxyethanol	0.5–1.0%		
Phenylethyl Alcohol	0.25–0.5%		
Phenylmercuric Nitrate	0.002–0.01%		
Propylene Glycol	15–30%		

solutions. Activity against bacteria can be variable because of its limited stability. Thus, sorbic acid is frequently used in combination with other antimicrobial preservatives or glycols in which synergistic effects occur.

Esters

Parabens are esters of *p*-hydroxybenzoic acid and include the methyl, ethyl, propyl, and butyl derivatives. The water solubility of the parabens decreases as the molecular weight increases from 0.25% for the methyl ester to 0.02% for the butyl ester. These compounds are used widely in pharmaceutical products, stable over a pH range of 4 to 8, and have a broad spectrum of antimicrobial activity, although they are most effective against yeasts and molds. Antimicrobial activity increases as the chain length of the alkyl moiety is increased, but aqueous solubility decreases; therefore, a mixture of parabens is frequently used to provide effective preservation. Preservative efficacy is also improved by the addition of propylene glycol (2–5%) or by using parabens in combination with other antimicrobial agents such as imidurea. Activity is reduced in the presence of nonionic surface active agents due to binding. In alkaline solutions, ionization takes place and this reduces their activity; in addition, hydrolytic decomposition of the ester group occurs with a loss of activity.

Quaternary Ammonium Compounds

Benzalkonium chloride is a mixture consisting principally of the homologs $C_{12}H_{25}$ and $C_{14}H_{29}$. This preservative is used at a relatively low concentration, 0.002% to 0.02%, depending on the nature of the pharmaceutical product. This class of compounds has an optimal activity over the pH range of 4 to 10 and is quite stable at room temperature. Because of the cationic nature of this type of preservative, it is incompatible with many anionic compounds such as surfactants and can bind to nonionic surfactants. It is used generally in preparations for external use or those solutions that come in contact with mucous membranes. In ophthalmic preparations, benzalkonium chloride is widely used at a concentration of 0.01–0.02% w/w. Often it is used in combination with other preservatives or excipients, particularly 0.1% w/v disodium edetate, to enhance its antimicrobial activity against strains of *Pseudomonas*. A concentration of 0.002–0.02% is used in nasal and otic formulations, sometimes in combination with 0.002–0.005% thimerosal. Benzalkonium chloride 0.01% w/v is also employed as a preservative in small-volume parenteral products.

Clearly, when the pharmacist dispenses or compounds liquid preparations, responsibility is assumed, along with the manufacturer, for the maintenance of product stability. General chapter ⟨1191⟩ of the USP describes stability considerations for dispensing, which should be studied in detail.[9] Stock should be rotated and replaced if expiration dates on the label so indicate. Products should be stored in the manner indicated on the manufacturer's label or in the compendium. Further, products should be checked for evidence of instability. With respect to solutions, elixirs, and syrups, major signs of instability are color change, precipitation, and evidence of microbial or chemical gas formation. Emulsions may cream, but if they break (ie, there is a separation of an oil phase) the product is considered unstable. Sedimentation and caking are primary indications of instability in suspensions. The presence of large particles may mean that excessive crystal growth has occurred (Ostwald Ripening). Additional details on these topics are provided in the pertinent sections of this chapter.

SOLUTIONS

A solution is a homogeneous mixture that is prepared by dissolving a solid, liquid, or gas in another liquid and represents a group of preparations in which the molecules of the solute or dissolved substance are dispersed among those of the solvent. Most solutions are unsaturated with the solute, in other words, the concentration of the solute in the solution is below its solubility limit. The strengths of pharmaceutical solutions are usually expressed in terms of % strength, although for very dilute preparations expressions of ratio strength are sometimes used. The term % when used without qualification (as with w/v, v/v, or w/w) means % weight-in-volume for solutions or suspensions of solids in liquids; % weight-in-volume for solutions of gases in liquids; % volume-in-volume for solutions of liquids in liquids; and % weight-in-weight for mixtures of solids and semisolids.

Solutions also may be classified on the basis of physical or chemical properties, method of preparation, use, physical state, number of ingredients, and particle size. For the pharmacist, solutions are more defined by site of administration and composition than by physicochemical definitions. For instance, pharmaceutical solutions may be classified as an *oral solution, nasal solution, ophthalmic solution,* or *topical solution*. These solutions may also be classified based upon their composition. *Syrups* are aqueous solutions containing a sugar; *elixirs* are sweetened hydroalcoholic (combinations of water and ethanol) solutions; *spirits* are solutions of aromatic materials if the solvent is alcoholic or *aromatic waters* if the solvent is aqueous. Depending on their method of preparation and concentration, *tinctures* or *fluid extracts* are solutions prepared by extracting active constituents from crude drugs.

Many pharmaceutical chemicals are only slowly soluble in a given solvent and require an extended time for complete dissolution. To increase the dissolution rate, a pharmacist may employ one or several techniques such as applying heat, reducing the particle size of the solute, utilizing of a solubilizing agent, or subjecting the ingredients to rigorous agitation. In most cases, solutes are more soluble in solvents at elevated temperatures than at room temperature or below due to the endothermic nature of the dissolution process. The pharmacist should ensure that the materials are heat stabile and non-volatile when using heat to facilitate the dissolution rate.

AQUEOUS SOLUTIONS

The narrower definition in this subsection limits the solvent to water and excludes those preparations that are sweet and/or viscid in character and nonaqueous solutions. This section includes those pharmaceutical forms that are designated as *Aromatic Waters, Aqueous Acids, Solutions, Douches, Enemas, Gargles, Mouthwashes, Juices, Nasal Solutions, Otic Solutions,* and *Irrigation Solutions.*

Aromatic Waters

The USP defines Aromatic Waters as clear, saturated aqueous solutions (unless otherwise specified) of volatile oils or other aromatic or volatile substances.[9] Their odors and tastes are similar, respectively, to those of the drugs or volatile substances from which they are prepared, and they are free from empyreumatic and other foreign odors. Aromatic waters may be prepared by distillation or solution of the aromatic substance, with or without the use of a dispersing agent. They are used principally as flavored or perfumed vehicles.

EXHIBIT C

The total paraben concentration fixed at 0.0375 % (m/V) is obtained with 0.3375 mg/ml of methyl parahydroxybenzoate and 0.0375 mg/ml of propyl parahydroxybenzoate.

The antimicrobial efficacy of the preservatives has been tested according to the European Pharmacopoeia 5.1.3 in order to demonstrate that the concentrations of preservatives (methyl parahydroxybenzoate and propyl parahydroxybenzoate) in Xyzal® 5 mg/ml oral drops are adequate to ensure the long-term protection of the drug product against microbial contamination.

Test for Efficacy of Antimicrobial Preservation

a) Efficacy of antimicrobial preservation at 100 % of the labeled strength of methylparaben (0.3375 mg/ml) and propylparaben (0.0375 mg/ml)

The efficacy of antimicrobial preservation has been tested according to the method of the European Pharmacopoeia on batches 11531, 11532, 03F30, 03K24 and 04B16. Batches 11531, 11532, 03K24 and 04B16 are also used in the stability study (see part 3.2.P.8). The results are summarized hereafter and demonstrate that the drug product complies with the requirements of the Ph. Eur. 5.1.3.

Table 2:5 **Batches Tested**

Batch number	Date of manufacture	Batch size (l)	Place of manufacture	Drug substance batch number	Drug substance batch size
11531	02/2002	100	UCB S.A. Chemin du Foriest B – 1420 Braine-l'Alleud Belgium	C01375-1006 (2001092401)	104 kg
11532	02/2002	100			
03F30	06/2003	100	UCB PHARMA S.p.A. Via Praglia, 15 I-10044 PIANEZZA (Torino) Italy	01G201002	384 kg
03K24	11/2003	1000		03G201006	378 kg
04B16	02/2004	500		03H201008	370 kg

Table 2:6 **Results of the enumerations of batch 11531 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	8.70×10^5	5.00×10^5	3.48×10^5	1.65×10^5	1.26×10^6
0	2.42×10^3	2.40×10^5	3.19×10^5	1.21×10^4	2.12×10^5
After 7 days	< 1	< 1	< 1	< 1	5×10^2
After 14 days	< 1	< 1	< 1	< 1	< 1
After 21 days	< 1	< 1	< 1	< 1	< 1
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:7 **Results of the enumerations of batch 11532 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	8.70×10^5	5.00×10^5	3.48×10^5	1.65×10^5	1.26×10^6
0	3.10×10^5	2.91×10^5	3.28×10^5	9.80×10^4	2.78×10^6
After 7 days	< 1	< 1	< 1	< 1	$< 10^3$
After 14 days	< 1	< 1	< 1	< 1	< 1
After 21 days	< 1	< 1	< 1	< 1	< 1
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:8 **Results of the enumerations of batch 03F30 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	6.90×10^5	3.85×10^5	4.35×10^5	4.55×10^5	1.56×10^6
0	5.35×10^5	2.85×10^5	3.65×10^5	4.30×10^5	1.38×10^6
After 7 days	< 1	< 1	< 1	< 1	4.50×10^2
After 14 days	< 1	< 1	< 1	< 1	< 1
After 21 days	< 1	< 1	< 1	< 1	< 1
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:9 **Results of the enumerations of batch 03K24 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	2.4×10^6	4.1×10^6	2.2×10^6	3.4×10^6	4×10^5
0	1×10^4	1.6×10^5	3.7×10^5	3.2×10^5	5×10^4
After 14 days	0	0	0	0	0
After 28 days	0	0	0	0	0

Table 2:10 **Results of the enumerations of batch 04B16 (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	2.1×10^6	2.1×10^6	1.2×10^6	3.1×10^6	4.1×10^6
0	1×10^5	1×10^5	3×10^5	1×10^5	3×10^5
After 14 days	0	0	0	0	0
After 28 days	0	0	0	0	0

b) Efficacy of antimicrobial preservation at *different concentrations* of methylparaben and propylparaben.

The efficacy of antimicrobial preservation has been tested on formulations containing the following concentrations of parabens :

- 0 mg/ml methylparahydroxybenzoate and 0 mg/ml propylparahydroxybenzoate
- 0.3375 mg/ml methylparahydroxybenzoate and 0.0375 mg/ml propylparahydroxybenzoate
- 0.675 mg/ml methylparahydroxybenzoate and 0.075 mg/ml propylparahydroxybenzoate
- 1.0125 mg/ml methylparahydroxybenzoate and 0.1125 mg/ml propylparahydroxybenzoate

The results are summarized hereafter and demonstrate that all formulations are in compliance with the requirements of the Ph. Eur. 5.1.3.

Table 2:11 **Results of the enumerations of batch 11294 0 mg/ml methylparahydroxybenzoate and 0 mg/ml propylparahydroxybenzoate (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.5×10^5	3.1×10^5	1.8×10^5	1.7×10^6
After 7 days	<100	<100	<100	<100	9.0×10^4
After 14 days	<1	<1	<1	<1	<1000
After 21 days	<1	<1	<1	<1	<1
After 28 days	<1	<1	<1	<1	<1

Table 2:12 **Results of the enumerations of batch 11295 0.3375 mg/ml methylparahydroxybenzoate and 0.0375 mg/ml propylparahydroxybenzoate (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.2×10^5	2.6×10^5	1.7×10^5	1.8×10^6
After 7 days	<100	<100	<100	<100	9.5×10^4
After 14 days	<1	<1	<1	<1	<1000
After 21 days	<1	<1	<1	<1	<1
After 28 days	<1	<1	<1	<1	<1

Table 2:13 **Results of the enumerations of batch 11296 0.675 mg/ml methylparahydroxybenzoate and 0.075 mg/ml propylparahydroxybenzoate (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.1×10^5	1.0×10^5	3.0×10^5	1.8×10^5	1.4×10^6
After 7 days	<100	<100	<100	<100	5.4×10^4
After 14 days	<1	<1	<1	<1	<1000
After 21 days	<1	<1	<1	<1	<1
After 28 days	<1	<1	<1	<1	<1

Table 2:14 **Results of the enumerations of batch 11297 1.0125 mg/ml methylparahydroxybenzoate and 0.1125 mg/ml propylparahydroxybenzoate (CFU per ml of product)**

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	2.9×10^5	6.9×10^4	2.7×10^5	5.0×10^4	1.5×10^6
After 7 days	<100	100	<100	<100	4.8×10^4
After 14 days	<1	<1	<1	<1	<1000
After 21 days	<1	<1	<1	<1	<1
After 28 days	<1	<1	<1	<1	<1

EXHIBIT D

The total paraben concentration fixed at 0.075 % (m/V) is obtained with 0.675 mg/ml of methyl parahydroxybenzoate and 0.075 mg/ml of propyl parahydroxybenzoate.

The antimicrobial efficacy of the preservatives has been tested according to the European Pharmacopoeia (5.1.3) in order to demonstrate that the concentrations of preservatives (methyl parahydroxybenzoate and propyl parahydroxybenzoate) in Xyzal 0.5 mg/ml oral solution are adequate to ensure the long-term protection of the drug product against microbial contamination.

Test for Efficacy of Antimicrobial Preservation

The efficacy of antimicrobial preservation has been tested according to the method of the European Pharmacopoeia on batches of Xyzal 0.5 mg/ml oral solution containing increasing concentrations in preservatives (0 %, 0.0375%, 0.075 % and 0.1125 % (m/V)).
The results are summarized hereafter and demonstrate that the drug product containing 0.075 % preservatives complies with the requirements of the Ph. Eur. (5.1.3).

Moreover, the results given in section 3.2.P.8 show the stability of the preservatives activity as supported by the antimicrobial preservatives efficacy test performed at time 0 and towards the end of the shelf life.

Table 2:3 Batches Tested

Batch number	Date of manufacture	Batch size (l)	Place of manufacture	Drug substance batch number	Drug substance batch size (kg)	Preservatives concentration (% m/V)
11298	09/2001	1	UCB S.A. Chemin du Foriest B – 1420 Braine-l'Alleud Belgium	507	11.4 kg	0
11299	09/2001	1		507	11.4 kg	0.0375
11300	09/2001	1		507	11.4 kg	0.075
11301	09/2001	1		507	11.4 kg	0.1125
11434 (02A09)	01/2002	1000	UCB Pharma S.p.A. Via Praglia, 15 I-10044 PIANEZZA (Torino) Italy	C01375 - 1006	104.3 kg	0.075
11435 (02A10)	01/2002	1000		C01375 - 1006	104.3 kg	0.075

Table 2:4 Results of the enumerations of batch 11298 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.2×10^5	1.8×10^5	3.5×10^5	3.9×10^5	1.6×10^6
After 7 days	150	< 100	< 100	2.8×10^4	1.0×10^6
After 14 days	< 1	< 1	< 1	1.4×10^4	4.8×10^5
After 21 days	< 1	< 1	< 1	2.6×10^2	2.2×10^5
After 28 days	< 1	< 1	< 1	6.2×10^3	5.3×10^5

Table 2:5 Results of the enumerations of batch 11299 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.7×10^5	1.3×10^5	2.8×10^5	3.8×10^5	1.6×10^6
After 7 days	< 100	< 100	< 100	2.0×10^4	1.1×10^6
After 14 days	< 1	< 1	< 1	1.7×10^4	1.6×10^5
After 21 days	< 1	< 1	< 1	30	7.0×10^3
After 28 days	< 1	< 1	< 1	< 1	< 100

Table 2:6 Results of the enumerations of batch 11300 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.5×10^5	1.6×10^5	2.4×10^5	3.4×10^5	1.6×10^6
After 7 days	< 100	< 100	< 100	4.3×10^3	1.3×10^6
After 14 days	< 1	< 1	< 1	5.5×10^2	1.4×10^4
After 21 days	< 1	< 1	< 1	< 1	4.0×10^2
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:7 Results of the enumerations of batch 11301 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	3.6×10^5	1.7×10^5	2.7×10^5	3.4×10^5	1.7×10^6
0	3.9×10^5	1.2×10^5	3.0×10^5	3.5×10^5	1.4×10^6
After 7 days	< 100	< 100	< 100	2.0×10^5	8.9×10^5
After 14 days	< 1	< 1	< 1	< 10	< 1000
After 21 days	< 1	< 1	< 1	< 1	< 1
After 28 days	< 1	< 1	< 1	< 1	< 1

Table 2:8 Results of the enumerations of batch 11434 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	1.04×10^5	3.44×10^5	5.65×10^5	9.35×10^5	1.98×10^6
0	4.25×10^4	2.48×10^5	3.85×10^5	5.70×10^5	1.90×10^6
After 7 days	< 100	< 100	< 100	2.85×10^4	8.00×10^4
After 14 days	< 1	< 1	< 1	50	4.65×10^4
After 21 days	< 1	< 1	< 1	< 1	50
After 28 days	< 1	< 1	< 1	< 1	100

Table 2:9 Results of the enumerations of batch 11435 (CFU per ml of product)

Time	Pseudomonas aeruginosa ATCC 9027	Escherichia coli ATCC 8739	Staphylococcus aureus ATCC 6538	Candida albicans ATCC 10231	Aspergillus niger ATCC 16404
Inoculum count	1.04×10^5	3.44×10^5	5.65×10^5	9.35×10^5	1.98×10^6
0	4.00×10^4	2.70×10^5	3.70×10^5	5.60×10^5	2.18×10^6
After 7 days	< 100	< 100	< 100	< 100	2.36×10^6
After 14 days	< 1	< 1	< 1	< 1	6.50×10^3
After 21 days	< 1	< 1	< 1	< 1	< 100
After 28 days	< 1	< 1	< 1	< 1	10